DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 27 Jan. 2012 has been entered.

Claims 1-21, 26, 27 and 29-43 are currently pending. Claims 1-21 are withdrawn. Claims 26, 27 and 29-43 are considered here.

Election/Restrictions

This application contains claims drawn to a non-elected invention. In the Response of 2 May 2011 Applicant elected the invention of Group II, drawn to a method of modulating a cholesterol level of a cell wherein the modulating increases or decreases the cholesterol level of the cell. Instant claims 26, 27 and 29-43 encompass methods of inducing re-localization of cholesterol from the plasma membrane to the endoplasmic reticulum or from the endoplasmic reticulum to the plasma membrane, independent of modulating (i.e. increasing or decreasing) the cholesterol level of the cell. A complete reply to the rejection must include cancellation of the nonelected claims and/or subject matter (See MPEP § 821.01). The pending claims are considered herein with respect to the elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26, 27 and 29-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of modulating a cholesterol level of a cell by contacting one or more cells with an effective amount of octanol for a sufficient time to decrease the total cholesterol level of the cell(s), does not reasonably provide enablement for such a method in which the cell(s) are contacted with an effective amount of octanol in combination with one or more of ceramide, diglyceride and lysophosphatidylcholine (LPC). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Whether a disclosure satisfies the enablement requirement is assessed with respect to the factors set forth in *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988); MPEP 2164.01 (a). These factors include: breadth of the claims, nature of the invention, state of the prior art, level of one of ordinary skill, level of predictability in the art, amount of direction provided by the inventor, existence of working examples and quantity of experimentation needed to make or use the invention.

All of the Wands factors have been considered with respect to the instant claims. The most relevant factors are discussed in detail below.

Breadth of the claims

The instant claims encompass methods of modulating a cholesterol level of a cell by contacting one or more cells with an effective amount of octanol or octanol in combination with one or more of ceramide, diglyceride and LPC for a sufficient time to decrease the total cholesterol level of the cell(s). Thus, in addition to octanol, the claims encompass seven different combinations containing octanol.

Level of predictability in the art

The effects of combinations of pharmacologically active agents on cells and more complex biological systems are highly unpredictable and must generally be determined empirically.

Amount of direction provided and Existence of working examples

The specification contains working examples (Specification, Examples 1-3, 5 and 6) in which cells are contacted with each of the claimed agents individually and the effects on the cholesterol activity of the cell are measured. Octanol, ceramide and diglyceride are shown to increase cholesterol activity (Specification, Figs. 1-3, 5 and 6) while LPC is shown to decrease cholesterol activity (Specification, Figs. 1 and 2). The specification hypothesizes that an increase in cholesterol activity "can result in an increase in the ER cholesterol pool size leading to a decrease in cell cholesterol minutes or hours later" (Specification, p. 13, lines 14-16) and that a decrease in cholesterol activity "can have the opposite effect" (Specification, p. 13, lines 16-17). The hypothesized effect on cell cholesterol levels is tested and shown only for octanol (Specification, Example 4; Fig. 4). There is no evidence that ceramide, diglyceride or LPC actually modulates cell cholesterol levels, either alone or in combination with

octanol. Moreover, since LPC is said to have an opposing effect on cell cholesterol to that of ceramide, diglyceride and octanol, it is unclear that combinations that include octanol and LPC would be effective at modulating cell cholesterol (e.g., LPC might cancel the effect of and/or inactivate octanol, ceramide and/or diglyceride). The specification also lacks any guidance on how a skilled artisan could go about carrying out the claimed methods using combinations of octanol and one or more of ceramide, diglyceride and LPC. For example, there is no guidance regarding specific combinations, effective amounts and sufficient times that would be effective in decreasing cell cholesterol. The specification also fails to describe how the claimed combinations should be administered (e.g., routes of administration, whether the components should be administered separately or co-administered and whether the various drugs are compatible for co-formulation).

Quantity of experimentation needed to make or use the invention

The lack of working examples and other guidance in the specification regarding the use of combinations of octanol and one or more of ceramide, diglyceride and LPC in the claimed methods would require a skilled artisan to undertake extensive and undue experimentation in order to practice the full scope of the invention.

Claim 27 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 27 is directed to a method of modulating cell cholesterol where the cell is *in vivo*. The specification does not provide any working examples showing that octanol, either alone or in combination with one or more of ceramide, diglyceride and LPC, is effective in modulating cell cholesterol *in vivo*. Octanol is known to be toxic to living cells (see e.g., Chen, et al., *FASEB J.* 15(9): 1649-51 (2001), 2nd ¶). Thus, it is unclear whether octanol or octanol-containing combinations could be effectively used *in vivo*. Example 7 of the specification indicates a variety of follow-up tests that should be conducted to determine the feasibility of using a cholesterol modulating agent of the invention *in vivo*. However, none of the tests has been conducted and the specification does not contain detailed guidance on how a skilled artisan would go about doing so. As such, a skilled artisan would be required to undertake extensive and undue experimentation in order to practice the invention of claim 27.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
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> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 26, 27 and 31-43 are rejected under 35 U.S.C. 102(b) as being inherently anticipated by Chen et al., *FASEB J.* 15(9): 1649-51 (2001).

Chen discloses a method of contacting cells of a mouse embryo (i.e. cells *in vivo*) with 1-octanol at concentrations ranging from about 1 µM to about 0.25 mM for a period

of 6 hours (p. 1649, 2nd ¶; p. 1650, Fig. 1A). An octanol concentration of 0.25 mM falls within the range shown in the specification to modulate cell cholesterol levels (Specification, Fig. 4; p. 17, lines 7-10). The claim limitation reciting a "sufficient time to ... decrease the total cholesterol level of the one or more cells" reads on the time period of 6 hours disclosed by Chen (cf. claims 35-37). Since the method of Chen meets all of the limitations of the claimed method, it would have necessarily resulted in the modulation of cellular cholesterol levels as recited in the instant claims.

Regarding claims 38-43, wherein modulating the cholesterol level increases or decreases susceptibility of the cell to cholesterol oxidation (claim 38) or to a lytic compound (claims 39-43), the specification indicates that increased or decreased susceptibility to cholesterol oxidation/lytic compounds is indicative of cholesterol activity and that octanol in the amount of 0.1-1.0 mM is sufficient to increase cholesterol activity (Specification, p. 14, lines 6-14; p. 16, lines 11-15; p. 17, lines 6-10). Since increased cholesterol activity gives rise to the claimed effect of lowering total cholesterol, a "sufficient time" to lower total cholesterol would necessarily also be sufficient to increase or decrease susceptibility to cholesterol oxidation/lytic compounds. Thus, the amount and duration of octanol treatment in Chen (which is within the ranges defined as sufficient to modulate cholesterol levels in the specification and claims) would be expected to give rise to the effects recited in claims 39-43.

Claims 26 and 30-43 are rejected under 35 U.S.C. 102(b) as being inherently anticipated by Ehrlich et al., *Journal of Cellular Physiology* 184(1): 86–92 (2000).

Ehrlich discloses a method of contacting human fibroblasts within a collagen lattice with 1-octanol at a concentration of 1 mM for a period of 18 hours (p. 88, Fig. 2A; p. 90, under Inclusion of uncouplers and FPCL contraction). An octanol concentration of 1 mM falls within the range shown in the specification to modulate cell cholesterol levels (Specification, Fig. 4; p. 17, lines 7-10). The claim limitation reciting a "sufficient time to ... decrease the total cholesterol level of the one or more cells" reads on the time period of 18 hours disclosed by Ehrlich (cf. claims 35-37). Since the method of Ehrlich meets all of the limitations of the claimed method, it would have necessarily resulted in the modulation of cellular cholesterol levels as recited in the instant claims.

Regarding claims 38-43, wherein modulating the cholesterol level increases or decreases susceptibility of the cell to cholesterol oxidation (claim 38) or to a lytic compound (claims 39-43), the specification indicates that increased or decreased susceptibility to cholesterol oxidation/lytic compounds is indicative of cholesterol activity and that octanol in the amount of 0.1-1.0 mM is sufficient to increase cholesterol activity (Specification, p. 14, lines 6-14; p. 16, lines 11-15; p. 17, lines 6-10). Since increased cholesterol activity gives rise to the claimed effect of lowering total cholesterol, a "sufficient time" to lower total cholesterol would necessarily also be sufficient to increase or decrease susceptibility to cholesterol oxidation/lytic compounds. Thus, the amount and duration of octanol treatment in Ehrlich (which is within the ranges defined as sufficient to modulate cholesterol levels in the specification and claims) would be expected to give rise to the effects recited in claims 39-43.

Claims 26, 29, 31-35 and 38-43 are rejected under 35 U.S.C. 102(b) as being inherently anticipated by Salesse et al., *Biochemistry* 21(7): 1587–1590 (1982).

Salesse discloses a method of contacting erythrocytes with 1-octanol at concentrations between 0.1 and 1.0 mM for a period of 20 minutes (p. 88, Fig. 2A; p. 90, under Inclusion of uncouplers and FPCL contraction). Octanol concentrations of 0.1-1.0 mM fall within the range shown in the specification to modulate cell cholesterol levels (Specification, Fig. 4; p. 17, lines 7-10). The claim limitation reciting a "sufficient time to ... decrease the total cholesterol level of the one or more cells" reads on the time period of 20 minutes disclosed by Salesse (cf. claim 35). Since the method of Salesse meets all of the limitations of the claimed method, it would have necessarily resulted in the modulation of cellular cholesterol levels as recited in the instant claims.

Regarding claims 38-43, wherein modulating the cholesterol level increases or decreases susceptibility of the cell to cholesterol oxidation (claim 38) or to a lytic compound (claims 39-43), the specification indicates that increased or decreased susceptibility to cholesterol oxidation/lytic compounds is indicative of cholesterol activity and that octanol in the amount of 0.1-1.0 mM is sufficient to increase cholesterol activity (Specification, p. 14, lines 6-14; p. 16, lines 11-15; p. 17, lines 6-10). Since increased cholesterol activity gives rise to the claimed effect of lowering total cholesterol, a "sufficient time" to lower total cholesterol would necessarily also be sufficient to increase or decrease susceptibility to cholesterol oxidation/lytic compounds. Thus, the amount and duration of octanol treatment in Salesse (which is within the ranges defined as

sufficient to modulate cholesterol levels in the specification and claims) would be expected to give rise to the effects recited in claims 39-43.

Response to Arguments

Applicant's arguments with respect to the rejection over Llinas have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT YAMASAKI whose telephone number is (571)270-5467. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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